ESMO IMMUNO-ONCOLOGY
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PRELIMINARY SAFETY AND EFFICACY OF ADAGRASIB WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING A KRAS^{G12C} MUTATION

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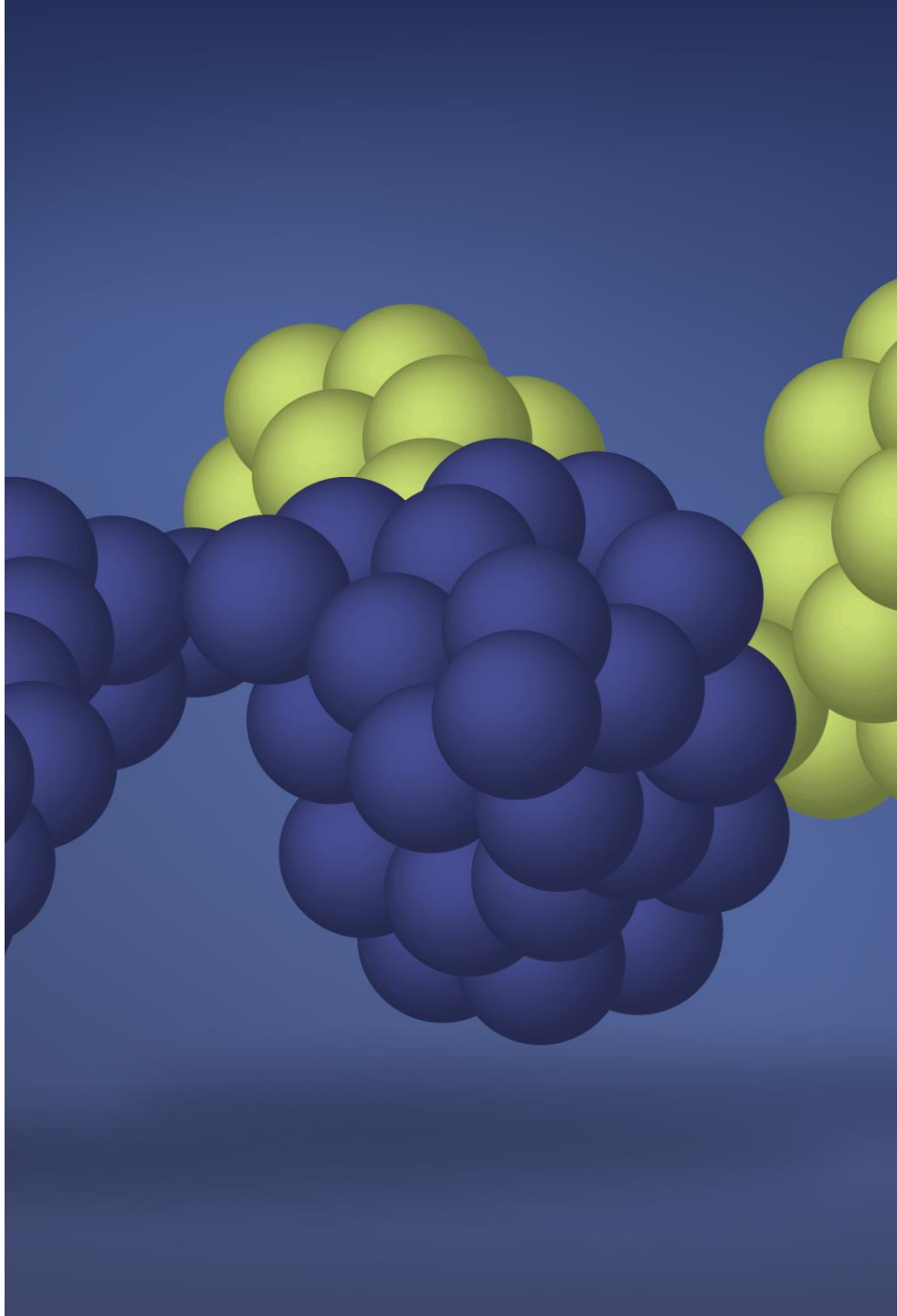
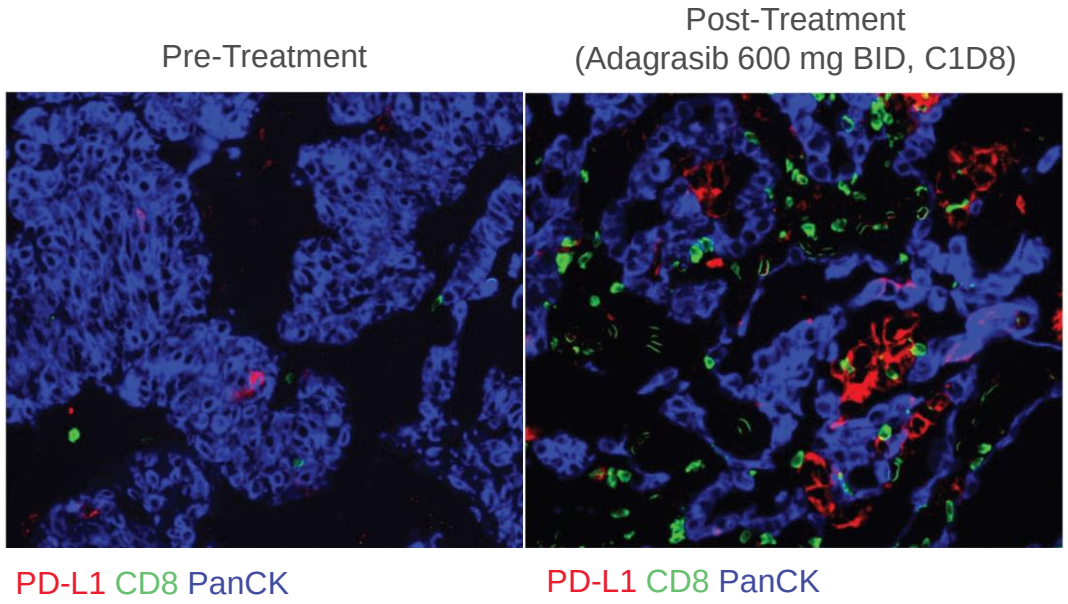


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor: Rationale for Combination with Immunotherapy

- KRAS^{G12C} mutations act as oncogenic drivers and occur in ~14% of patients with NSCLC (adenocarcinoma)[1]
- Adagrasib, an inhibitor of KRAS^{G12C}, was selected for desired properties, including a long half-life (23 hours), dose-dependent PK and CNS penetration[2,3,4]
- Clinical activity with adagrasib has been shown in patients in multiple KRAS^{G12C}-mutated solid tumors including patients with NSCLC and either stable/treated or untreated CNS metastases[4–9]
- Several data support combination of adagrasib and immunotherapy
  - Adagrasib plus an anti-PD1 antibody demonstrated increased immune response and efficacy in preclinical models[10]
  - An increase in innate and adaptive immune responses has been observed in tumors from patients treated with adagrasib[11]

Increased CD8 T-Cell Responses in Adagrasib Post-Treatment Biopsies[11]



KRYSTAL-1 (849-001) Phase 1b and KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease
- Stable brain metastases allowed

KRYSTAL-1 Phase 1b

Adagrasib 400 mg[b] BID + Pembrolizumab
N=7

Key Study Objectives

- Primary endpoint: safety
- Secondary endpoints: ORR (RECIST v1.1), DOR, PFS, OS

KRYSTAL-7 Phase 2

Cohort 1a, PD-L1 TPS <1%[c,d]
Adagrasib 400 mg BID + Pembrolizumab
N=11

Cohort 2, PD-L1 TPS ≥1%[c]
Adagrasib 400 mg BID + Pembrolizumab
N=64

Key Study Objectives

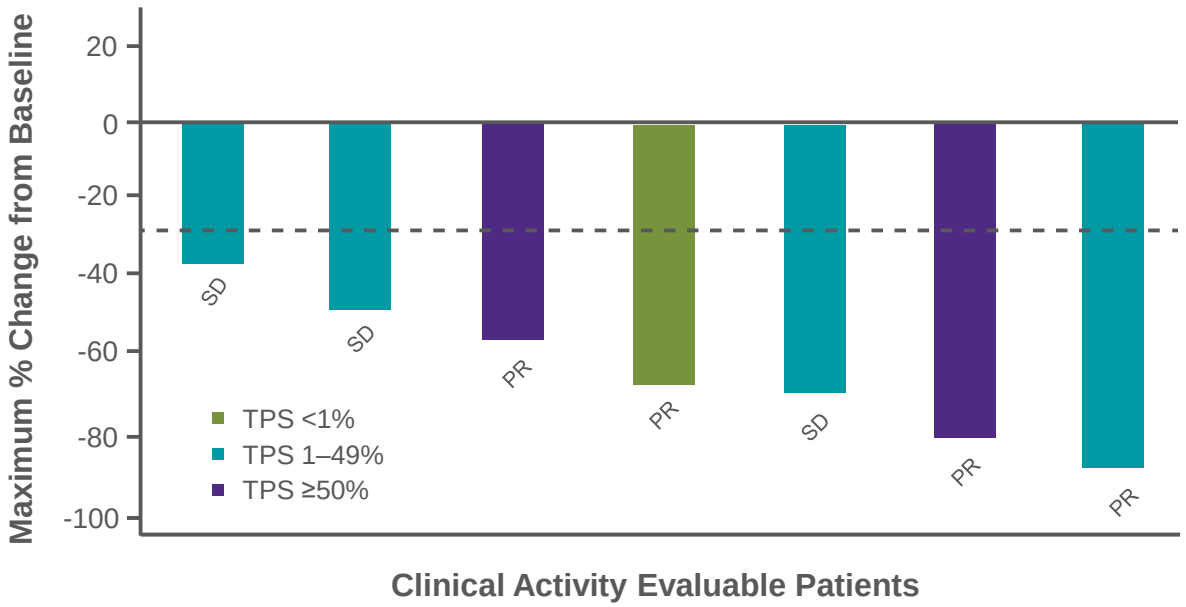
- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoints: DOR, PFS, OS, safety, PK

- We report preliminary safety and efficacy data from a phase 1b cohort of KRYSTAL-1 and the phase 2 KRYSTAL-7 studies, evaluating adagrasib[e] 400 mg BID + pembrolizumab 200 mg IV Q3W in treatment-naïve patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- KRYSTAL-1 median follow-up, 19.3 months; KRYSTAL-7 median follow-up 3.5 months

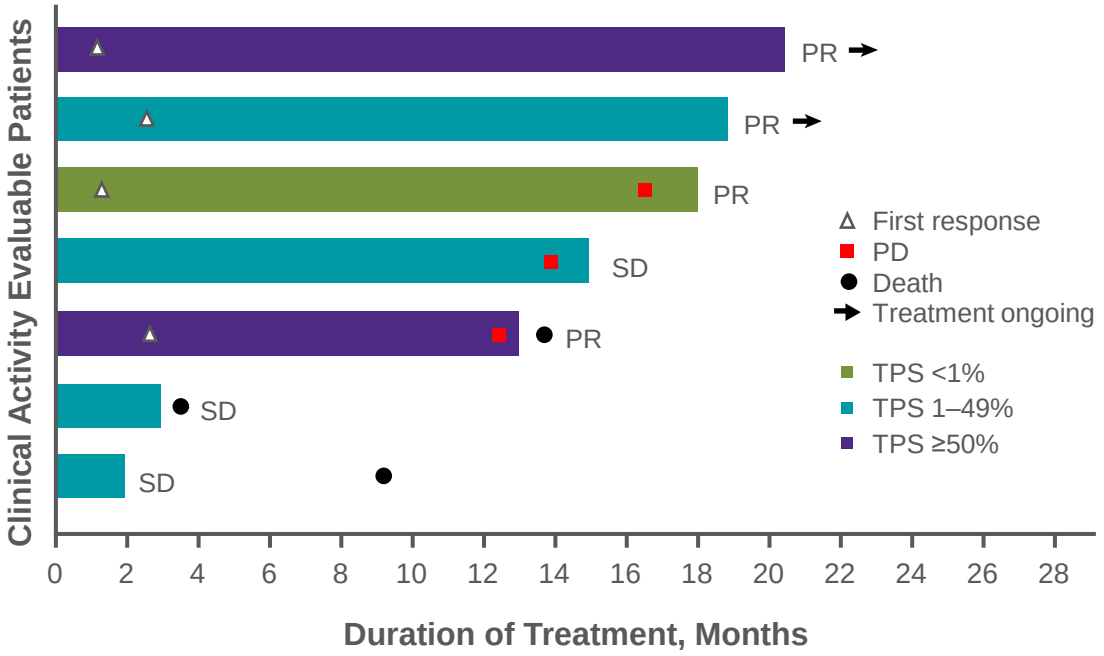
[a]$KRAS^{G12C}$ mutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing per protocol. [b]KRYSTAL-1 phase 1b cohort was initiated using 600 mg BID adagrasib dosing and switched to 400 mg BID dosing during study conduct. [c]Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory and test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). [d]An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. [e]KRYSTAL-7 was initiated using the capsule (fasted) formulation of adagrasib but switched to the tablet (fed or fasted) formulation during study conduct ClinicalTrials.gov. NCT04613596

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-1 (Phase 1b) Tumor Response

Best Tumor Change from Baseline (n=7)



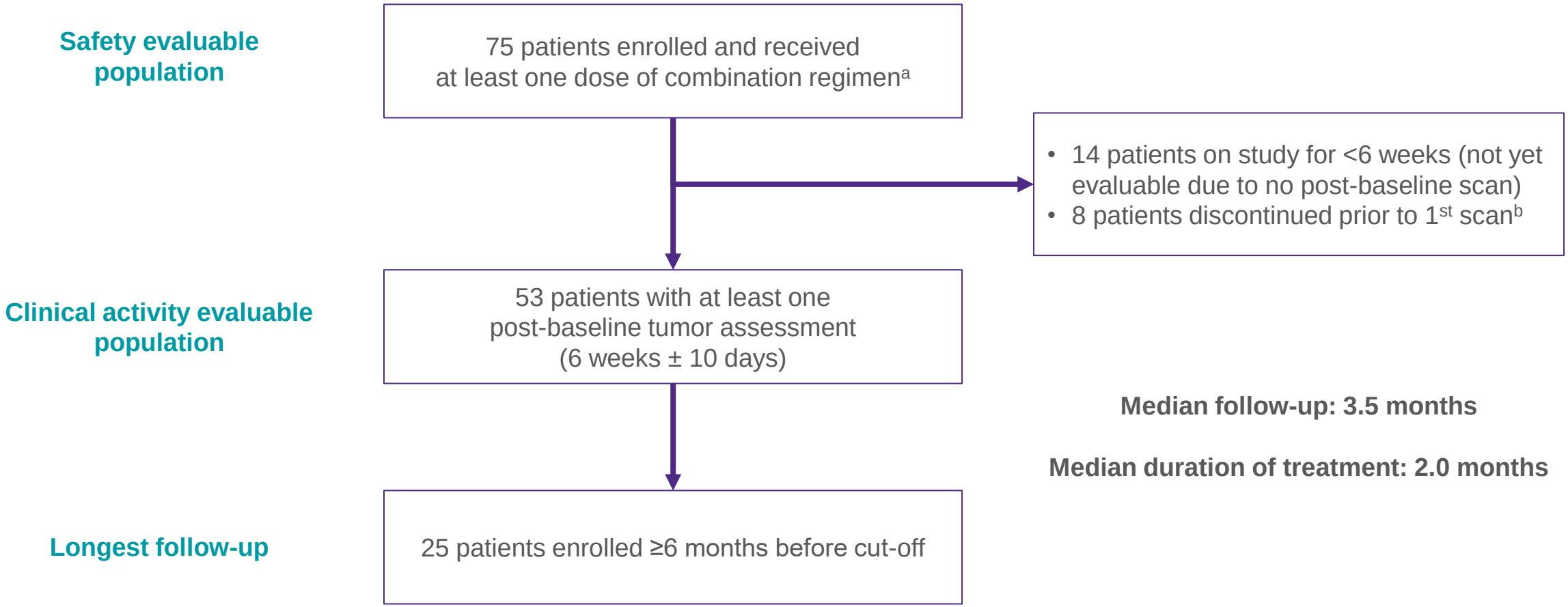
Duration of Treatment (n=7)



- Objective responses were observed in 57% (4/7)[a] of patients across all PD-L1 levels, with a disease control rate of 100%
- Responses were observed in 2/2 patients with PD-L1 TPS ≥50%, 1/4 with PD-L1 TPS 1–49%, and 1/1 with PD-L1 TPS <1%
- All 4 patients who responded had a durable response >9 months, with 2 still receiving treatment beyond 18 months
- Grade 3 TRAEs were seen in 4 patients[b]; there were no grade 4 or 5 TRAEs

[a]One additional patient experienced a 49% tumor regression, which allowed for tumor resection prior to achieving RECIST-defined confirmed response. [b]Lipase increased (n=1); ALT increased, AST increased, alkaline phosphatase increased (n=1); musculoskeletal pain (n=1); pneumothorax (n=1)
Data as of 30 August, 2022. Median follow-up 19.3 months

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Patient Flow



[a]Pooled patients from cohort 1a PD-L1 TPS <1% and cohort 2 PD-L1 TPS ≥1%. [b]Discontinued due to death not related to treatment (n=5), lost to follow-up (n=1), adverse event not related to treatment (n=1), global deterioration of health (n=1)
Data as of 30 August, 2022

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Demographics and Baseline Characteristics

	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)
Median age (range), years	66 (40–84)
Female, n (%)	38 (51)
Race, n (%)	
White	67 (89)
Black or African American	5 (7)
Asian / Other	3 (4)
ECOG PS, n (%)	
0 / 1	26 (35) / 49 (65)
PD-L1 status, n (%)	
<1%	11 (15)
1–49%	28 (37)
≥50%	36 (48)
Smoking history, n (%)	
Never smoker	1 (1)
Current smoker / former smoker	74 (99)
Baseline metastases, n (%)	
Bone	30 (40)
CNS	9 (12)
Adrenal	10 (13)
Liver	15 (20)

72 (96%) patients had adenocarcinoma, 1 (1%) had squamous histology, and 2 (3%) had unclassified/undifferentiated carcinoma
Data as of 30 August, 2022. Median follow-up 3.5 months

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Treatment-Related Adverse Events

Most Frequent TRAEs	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=75)				
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TRAEs	83%	15%	24%	40%	4%[a]
Most frequent TRAEs[b], %					
Nausea	48%	24%	19%	5%	0%
Diarrhea	43%	33%	5%	4%	0%
Vomiting	24%	13%	9%	1%	0%
ALT increased	21%	7%	7%	8%	0%
AST increased	21%	7%	5%	9%	0%
Fatigue	21%	9%	8%	4%	0%
Decreased appetite	20%	11%	9%	0%	0%
Amylase increased	16%	5%	11%	0%	0%

- There were no Grade 5 TRAEs
- Median time to onset for ALT increase and AST increase was 26 and 37 days, respectively; only 1 patient experienced new onset treatment-related ALT/AST increase after 3 months
- TRAEs led to adagrasib dose reduction in 23/75 (31%) patients and to dose interruption in 31/75 (41%) patients
- TRAEs led to discontinuation of both drugs in 2/75 (3%) patients and only pembrolizumab in 2/75 (3%)[c] patients

[a]Gr 4 TRAEs comprised 1 case each of pneumonitis, neutropenia and pulmonary embolism. [b]Occurring in >15% of patients (any grade). Additional TRAEs of interest include 1 (1%) patient with Gr 1 blood bilirubin increased, 1 (1%) with Gr 2 pancreatitis, 2 (3%) with Gr 3 hepatitis, 8 (11%) with Gr 3 lipase increased, 2 (3%) with Gr 3–4 pneumonitis, and 2 (3%) with Gr 1–2 QT prolongation. [c]No patients discontinued only adagrasib due to a TRAE
Data as of 30 August, 2022. Median follow-up 3.5 months. Median duration of treatment 2.0 months

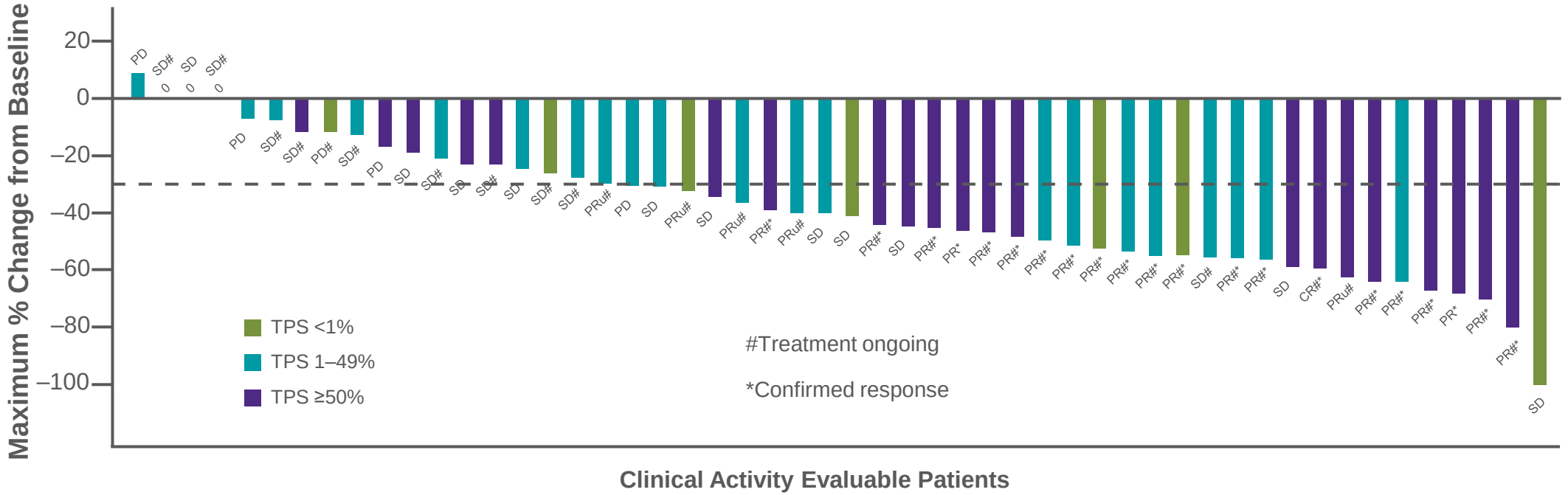
Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Tumor Response

	Concurrent 400 mg BID Adagrasib + Pembrolizumab (n=53)[a,b]
Objective response rate, n (%)	26 (49)
95% CI	35–63
Best overall response, n (%)	
Complete response	1 (2)
Partial response	25 (47)
Stable disease	21 (40)
Progressive disease	6 (11)
Disease control rate, n (%)	47 (89)
95% CI	77–96

- ORR includes confirmed and unconfirmed CR/PR; 2 PRs were confirmed after data cut-off, and 3 responses remain unconfirmed, but patients remain on treatment

[a]Clinical activity evaluable population includes patients who received at least one dose of adagrasib (400 mg BID) + pembrolizumab and had measurable disease at baseline and at least one post-baseline tumor assessment. [b]In the clinical evaluable population including patients who discontinued prior to first scan for reasons not related to treatment (n=61), ORR was 43% (26/61)
Data as of 30 August, 2022. Median follow-up 3.5 months. Median duration of treatment 2.0 months

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Best Tumor Change from Baseline



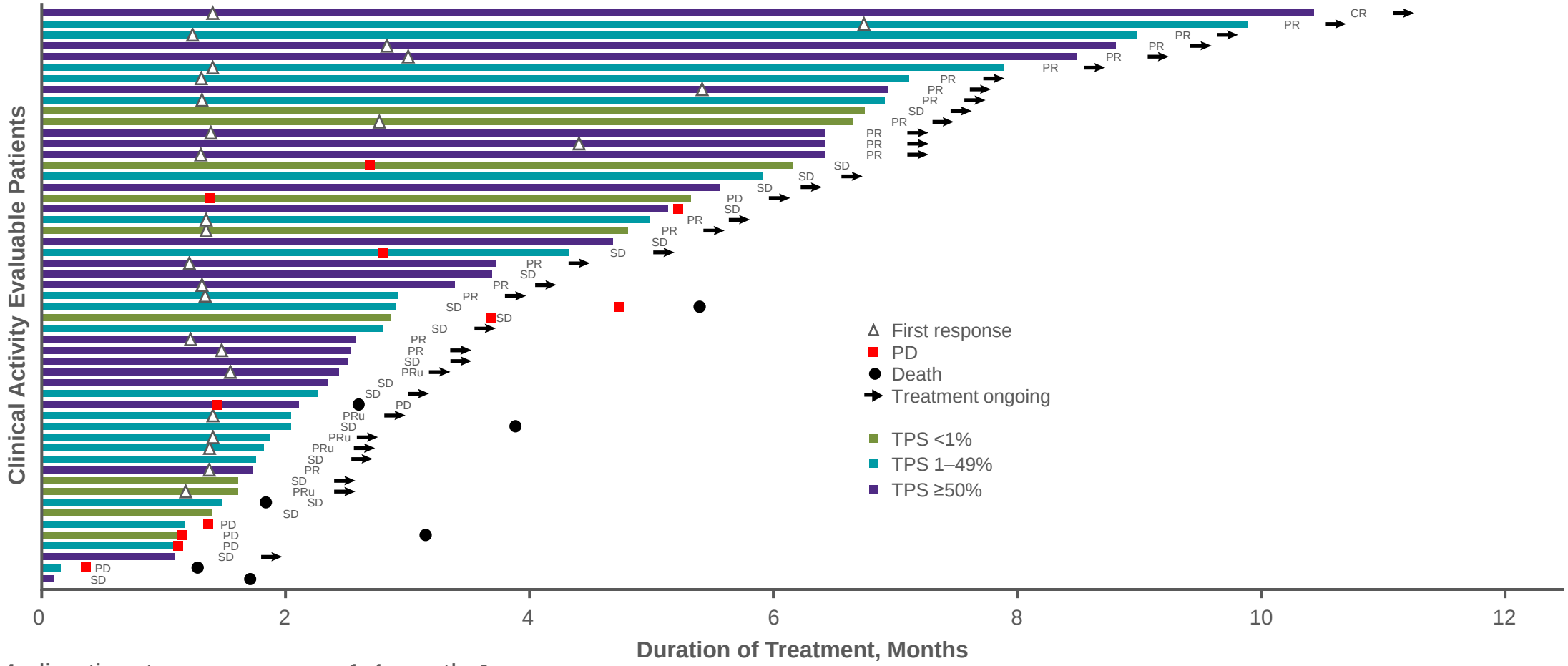
- Objective responses were observed in 49% (26/53)[a] of patients across all PD-L1 levels, with a disease control rate of 89% (47/53)
- Responses were observed in 59% (13/22)[a] of patients with PD-L1 TPS ≥50%, 48% (10/21)[a] with PD-L1 TPS 1–49%, and 30% (3/10)[a] with PD-L1 TPS <1%

Clinical activity evaluable population (n=53). One patient had only one post-baseline tumor assessment of PD due to new lesion; target lesions were not measured, therefore not included in the plot. Responses include target lesion tumor regression, as well as non-target lesion assessment

[a]Includes confirmed and unconfirmed CR/PR

Data as of 30 August, 2022. Median follow-up 3.5 months

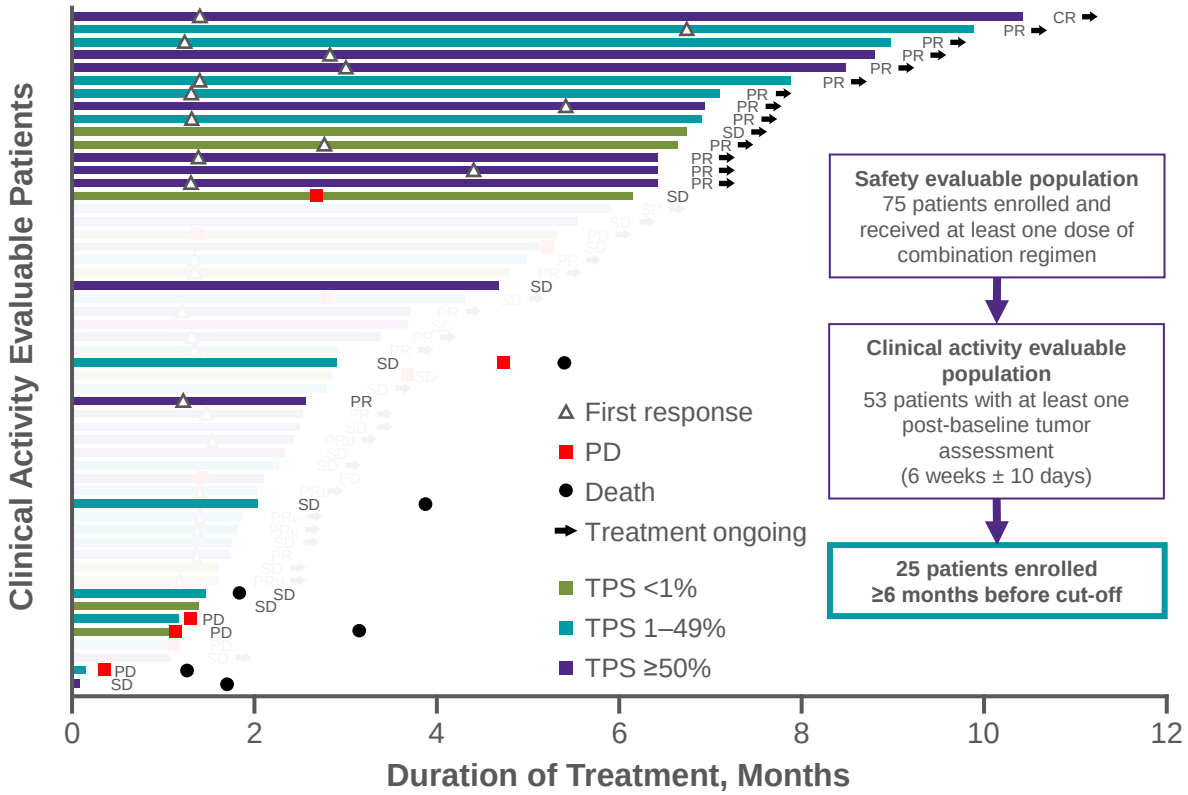
Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Duration of Treatment



- Median time to response was 1.4 months[a]
- Of 26 patients who responded, 6 achieved response after >2 months of treatment
- Treatment is ongoing in 66% (35/53) of patients, including in 24 patients with response

Clinical activity evaluable population (n=53). [a]Based on confirmed responses
Data as of 30 August, 2022. Median follow-up 3.5 months

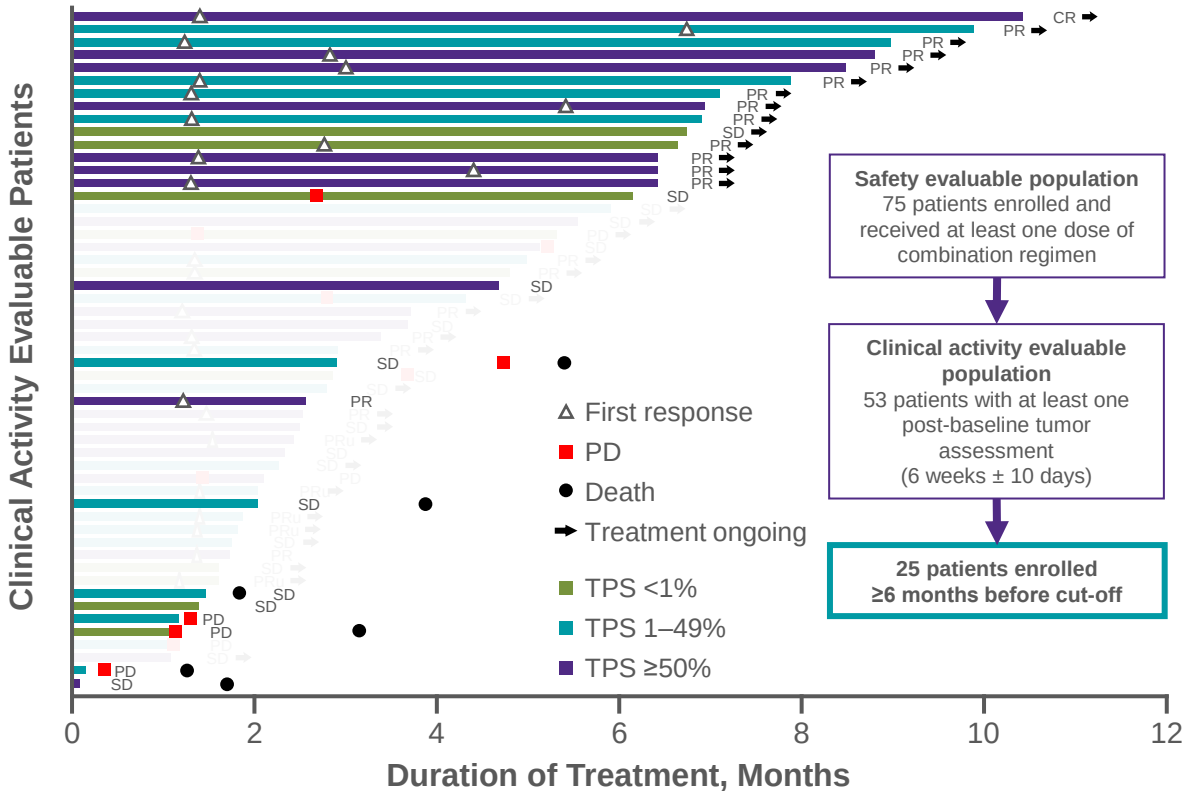
Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Efficacy in Patients Enrolled for ≥6 months

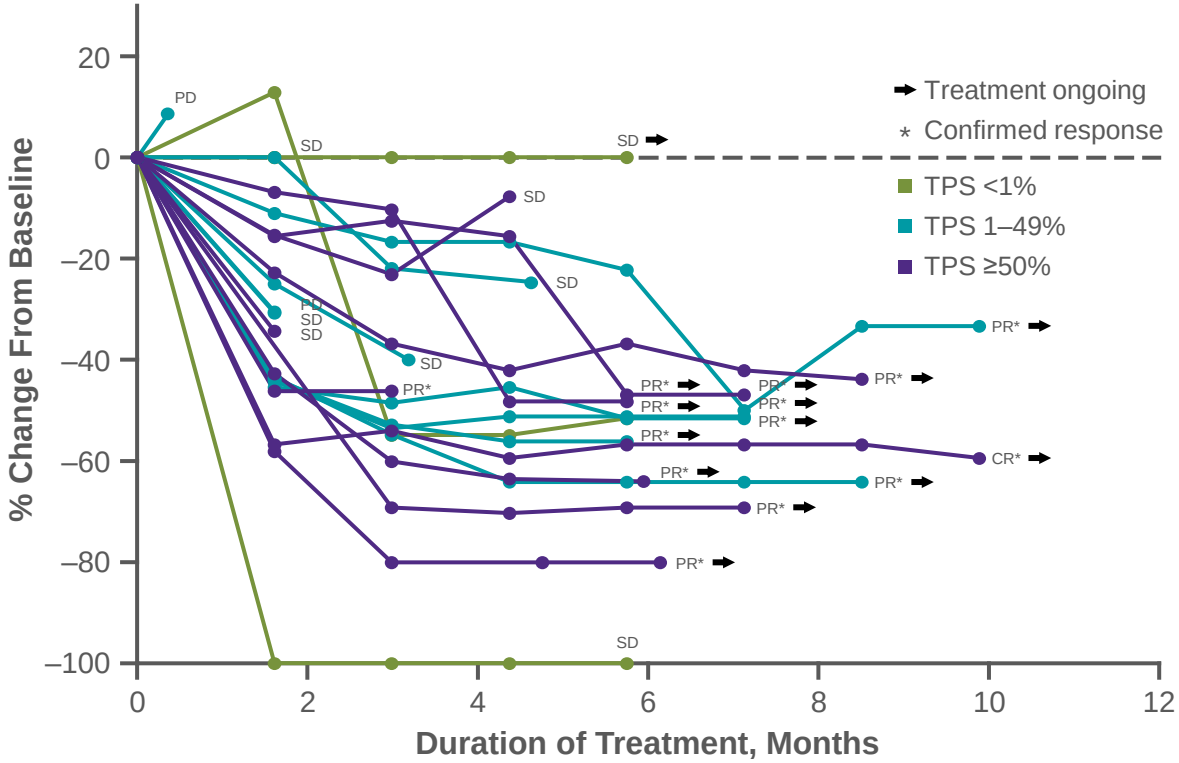


- For clinical activity evaluable patients who were enrolled ≥6 months before data cut-off, ORR was 56% (14/25)

Clinical activity evaluable population who were enrolled ≥6 months before data cut-off (n=25)
Data as of 30 August, 2022. Median follow-up 3.5 months

Adagrasib + Pembrolizumab in Treatment-Naïve KRAS^{G12C}-mutated NSCLC: KRYSTAL-7 Efficacy in Patients Enrolled for ≥6 months





- For clinical activity evaluable patients who were enrolled ≥6 months before data cut-off, ORR was 56% (14/25)

Clinical activity evaluable population who were enrolled ≥6 months before data cut-off (n=25)
Data as of 30 August, 2022. Median follow-up 3.5 months

Conclusions

- The KRYSTAL-1 and KRYSTAL-7 trials evaluating concurrent adagrasib + pembrolizumab are the largest dataset evaluating a $KRAS^{G12C}$ inhibitor in combination with a PD-1/L1 checkpoint inhibitor as first-line treatment for patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- In this preliminary analysis, concurrent adagrasib + pembrolizumab had a manageable safety profile, consistent with either agent as monotherapy, and with a low rate of TRAEs leading to discontinuation
- Liver-related TRAEs were predominantly low grade, occurred early in treatment, and only one patient experienced new onset after 3 months
- Adagrasib + pembrolizumab demonstrated promising preliminary activity across all PD-L1 subgroups
- Based on these findings, Phase 3 trials are planned in first-line NSCLC, evaluating concurrent adagrasib 400 mg BID + pembrolizumab versus standard-of-care by PD-L1 status

For more information contact Mirati Medical Information at medinfo@mirati.com

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Abbreviations

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BID, twice daily

C1, cycle 1

CI, confidence interval

CNS, central nervous system

CR, complete response

ctDNA, circulating tumor deoxyribonucleic acid

D8, day 8

DOR, duration of response

ECOG PS, Eastern Cooperative Oncology Group Performance Status

Gr, grade

IHC, immunohistochemistry

IV, intravenous

KRAS, Kirsten rat sarcoma

NSCLC, non-small cell lung cancer

ORR, objective response rate

OS, overall survival

PD, progressive disease

PD-1, programmed cell death protein-1

PD-L1, programmed cell death ligand 1

PFS, progression-free survival

PK, pharmacokinetics

PR, partial response

Q3W, every 3 weeks

RECIST v1.1, response evaluation criteria in solid tumors version 1.1

SD, stable disease

TPS, tumor proportion score

TRAE, treatment-related adverse event